Attorney Docket No. 029318-0972

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:

Rajecv A. JAIN et al.

Title:

RAPIDLY DISINTEGRATING SOLID ORAL DOSAGE FORM

Appl. No.:

10/667,470

Filing Date:

9/23/2003

Examiner:

Brian Yong S. Kwon

Art Unit:

1614

Confirmation

9048

Number:

DECLARATION UNDER 37 C.F.R. §1.131

Sir:

- I, Stephen B. Ruddy, hereby declare and state that:
- 1. I am a citizen of the United States of America residing at 226 Stallion Lane, Schwenksville, Pennsylvania, U.S.A.
- 2. Currently I am a Senior Director of NanoCrystal Technology Product Development at Elan Drug Delivery, Inc., with offices at 3500 Horizon Drive, King of Prussia, PA 19406.
- 3. I am a co-inventor of the invention disclosed and claimed in the above-referenced application.
- 4. The claimed invention directed to preparing an oral solid dose of a rapidly disintegrating nanoparticulate active agent formulation was reduced to practice prior to May 27, 1999. The work relating to preparing the claimed formulation, which occurred prior to May 27, 1999, is documented in the attached exhibits.
- 5. As shown in Exhibit A (Notebook No. 5611, page 55), a nanoparticulate dispersion composition, comprising 20% IC-351 (a PDE5 inhibitor) as the active agent, and 4% hydroxypropyl

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methylcellulose (HPMC) and 0.2% sodium lauryl sulfate (SLS) as the surface stabilizers, and having an effective average particle size of from about 117 nm to about 124 nm, was prepared as a first step in producing a rapidly disintegrating nanoparticulate active agent composition.

- 6. As shown in Exhibit B (Notebook No. 5611, pages 56-57), the nanoparticulate dispersion composition described in Exhibit A was combined with mannitol (drug:mannitol ratio of 1:4), and the resulting composition was spray dried as a second step in producing a rapidly disintegrating nanoparticulate active agent composition.
- 7. As shown in Exhibit C (Notebook No. 5611, pages 68-69), the spray dried powder composition described in Exhibit B was combined with sodium bicarbonate, citric acid, sodium saccharin, magnesium stearate, silica, PVP K-90 and spray dried lactose. The resulting composition was then compressed into tablets on a Carver press as a final step in producing a rapidly disintegrating nanoparticulate active agent composition.
- 8. I further declare that all statements made herein of my knowledge are true and that all statements made on information and belief are believed to be true; and further, that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent resulting therefrom.

Stephen B Ruddy

Date

EXHIBIT A

NanoSystems™ LABORATORY NOTEBOOK NO. 5611 Page 055 of 200
Title_IC-351 fact-mell- taper project-
(cont. from pg. <u>054</u>)
Ain: - Filtering of IC-351 disperses
Method? - 1 kg of Dun-5612-116 (20% IC-151, 4% Hpmr, 0-2% JES) was filtered through a lodger filtered through a lodger filtered dysperson would then be mixed with named and spray-dried. The particle size of the dispersion (RAT-56H-055) was cheeked on Horiba LA-910.
HORIBA LA-910 for Windows(TM) Ver. 1.31 Ft Least scalabring particle size distribution energy are restricted for the size of t
Date Median
10 10 10 10 10 10 10 10 10 10 10 10 10 1
CONFIDENTIAL Signature Reviewed and understood by Cont. on pg. 056 Reviewed and understood by Date

EXHIBIT B

(cont. from pg. 055) April - Spray-drysy of TC-351 dispersion
(cont. from pg. 055) April Spray-Drysy of TC-351 dispersion
Ami Spray-drysy of IC-351 dispersion
Metrod: RAJ-5611-055 was mined with namitol and Spry and as follows:
400 g dispersion (RAJ-5611-055) + 1280 g water +320g mannito)
A lo dong/16 % marmilo.
The drug: manufol sofio will be 64 1972 320g of mannifol was dissolved to gently hearry and strong in 1280 g of water. On cooling this solm. to soon temperature, goog of mannifol was added and the dispersion was supprisonally stronger (RAS-5611-056)
This was beg spray-dried unit the Yamah Spray
The sampes were collected of various time intervels and cheeks for religions of chy in waters 11:45,92 OND 4:05 pai -> RAJ-5611-056B
2:40 pm -> RAJ-5611-056 C
4:05 m -> RAJ-5611-056D
5:20 pm -> RAJ-5611-056 E
CONFIDENTIAL Signature Reviewed and understood by (cont. on pg. 057) Date Date

Manosystems L	ABORATO	RY NOT	EBOOK NO. 36 I	Page 057 01 200
Title IC-35) for	a — saclli	ا لما	noise project	·
Title	7 - 0,00	70.0	1 1 1	
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(cont. from pg. <u>056</u>)			\ 	
(cont. nom par	and the second of the second section of the second sections.			
YAMATO F	PROCESSING INFO	RMATION		and a second contract of the second contract
Product: IC-35	Date.		11 RAJ-5611-	to a majoritation desired and a sum of the second s
Nozzie S	Size:		Processing Gas: Nitrogen	Particular and a commence of the first of th
Pump Type: <u>Masterflex</u> Pump Head: 70 Inlet Temperature Set Point (°C): 130 deg C	221-24 Set Pol	Tubing Size: Int (kgf/cm²):	2.2	
Inlet Temperature Set Point (*C): 130 day 5				
	emp Drying Ga Volume (m³/n	a Pulsa		
Time Pump Inlet Temp. Outlet T (minutes) Setting (°C) -(°C)	Volume (m*/i	min) (On/C		programme of the latter are the latter of th
11:45 - 9.0 128 50	0.30		cheeted for many min	14
1:30 pm 10:0 128 A8	0.4)		C(RAJ-5611-056)	2)
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2:10 h 10:0 130 52	2 3 9 to c	ean the	w221/e	
2 30 100 130 53	2 chet no	1195564	of lander in weeks	
7.60 10.00 150 5	4 0.39	- 		
3: 20' 10:0 129 5:	2 montes to	clean +	L ng 24c	an agentura ping ping all as jugad again-maylangagangangan ay ay akan akan ay akan
3.23				المراجعة والمراجعة والمراجع
YAMATO PROC	ESSING INFORMA		200	emplanders durings in a sur our own distings to hair our straight or a survival surprise state foresteen
Product: TC-35) Date			AJ-56 - seing Cas: <u>Nitrogen</u>	Ex alle dispressioners or the surfrightly provide serving the property of the serving of the ser
Spray Configuration: Spray Drying Nozzle Size: Pump Type: Masterflex Pump Head: 7021-24	Tub		100-14	
	ulon Air Set Point (kg		2.2	
Sample ID:				to the transport of the second
Time Pump Inlet Temp. Outlet Temp (minutes) Setting (°C) (°C)	Drying Gas Volume (m³/min)	Pulsa Jet (On/Off))	Comments / Observations	P
0	0.37			the stand statement with the statement of the statement o
3:45 h clean to 4020 - by	change wat	r fer	stratour for 22in	Appear operating the same or announced interesting the 1-year operation becomes the property of the continues of
4:00 10:0 130 58 4:05 5000 wake 20 change	e the pution	friter	(RAO-361)-056B)	provide the street and deposits of the street and the street and street an experience of deposits pain basis graining
1:15 16.0 129 5/0	0.38	<u> </u>	spring who for 222	the last state of the analysis of the said
4:45 10.0 129 58°	0.40		stand week for 200	I am the September of the Colombia and a september 2 because the development with the September and the colombia and deposit of the colombia a
5:10 10:0 129 59 5:15 10:0 130 59	0:40		child water for 2 mg.	
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5:20 Smay weter for 5 mm.	o clean ta	pule	(KAJ-S611-056E)	058

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Signature

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(cont. on pg._

Date

Date

EXHIBIT C

INDITION LABORATORY NOTEBOOK NO. 5611 Page 068 of 200
Title IC-351 fan-well taken project
Title IC35) far-nell table- project
(cont. from pg. <u>067</u>)
Ami-Preparation of roposoffast melting tablets of IC-351
Method;
The TC-95) fast meeting tesper is intended to
disntegate in less than 30 sec. The handness of the tablet would be in the sange of 1-4 PP.
Be ICO3 SDI (RAJ-5611-060) will be trad to
formulate - tee tablets. RAJ-5611-060 Contains 1900 dry (IC-251) 48%
Hemc/ marmarot) 76 % mannito 1 als 0'2% SLS.
A long dose taket is intended for this use.
The SDT would be combined with different encipients.
and blander, follower by light compression to give
the time time the tim
Sodium breasonate for Baker (lot # 3506-05) Plans Plasidone K-90 (Prindone VSP) from ISP Tehnologies (lot # A 70502)
Plasagne K-90 (Prinding V3P) from IST lehnologies (Col # A 10302)
Ciani acid Monety drate from Baker (Lot # F01711)
Saceham Soldin from Boker (10+#1733637)
(ab-0-si) (aportion siles) from (abot (orp. (Lot # 1)226)
Spray-dried Lactose from (Lot#)
Exicht Silica all the above crubicuts were
Sioned through 40 # They were Gentle in difference
proportions (60)
CONFIDENTIAL Signature Royew Jain Date
Reviewed and understood by Date

Title IC-351 fan-2	neur tabler b	rojeu-
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(cont. from pg. <u>068</u>)	£	
(cont. from pg)	and quantitative control of the state of the	ter francisco de Albrica dos estas portantes estas estas estas de la composition della composition del
The second secon	for I table.	: For low tapes
I(O) SDI	52.6 mg	5-260 9
Cod. Licar bente	30 mg	3.0 g
Ofre and	30 29	3.0 g 1.0 g
Sacchann Na	10 mg	75 20
Mohemm Hearde	1.4 mg	75 mg
5, li Ca pvp 1c-90	5 29	500 27
Spay-dia lactose	20:25 mg	2·025 g
week a series of the series of	150 ng	1500 g
SMA () B. W. C. B. Was sent the problem above and the sent whole we specify a property and because the constitution of the co		
Freebr Silice	2 an map steam	te all the above
excitate were by	ada in a V	te all the above
Gille Jer 30	in tracy a	minume en graca
and makeing	stearate was ad	di te Breson
(RAJ-5611-069)	was ready to	compression
	U	
Tablets seigning 150	ng were suparie	using the automated
Carrer pres and) URAJ-5617-069	
The press was J.	disch tize Dieco	However The
Cotral Costranto	n force Juny	Conformin was found
to be dus	pm. Be tolet	had havings is
the safe of	3-4 kg, Howeve	2 The the estates
trenggous Capping	and specing to	PVP K-90,
(out be the	To the use of	
	0	(cont. on pg. <u>070</u>)
CONFIDENTIAL	ture Kyew Jain	Date_
Reviewed and understoo	d by Trides	Zkr Date